

Performance of Empirical Potentials (AMBER, CFF95, CVFF, CHARMM, OPLS, POLTEV), Semiempirical Quantum Chemical Methods (AM1, MNDO/M, PM3), and *Ab Initio* Hartree–Fock Method for Interaction of DNA Bases: Comparison with Nonempirical Beyond Hartree–Fock Results

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ABSTRACT: Empirical energy functions (AMBER 4.1, CFF95, CHARMM23, OPLS, Poltev), semiempirical quantum chemical methods (AM1, MNDO/M, PM3), and the nonempirical *ab initio* self-consistent field (SCF) method utilizing a minimal basis set combined with the London dispersion energy (SCFD method) were used for calculation of stabilization energies of 26 H-bonded DNA base pairs, 10 stacked DNA base pairs (thymine was replaced by uracil), and the B-DNA decamer (only DNA bases were considered). These energies were compared with nonempirical *ab initio* beyond Hartree–Fock values [second-order Møller–Plesset (MP2)/6–31G*(0.25)]. The best performance was

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exhibited by AMBER 4.1 with the force field of Cornell et al. The SCFD method, tested for H-bonded pairs only, exhibited stabilization energies that were too large. Semiempirical quantum chemical methods gave poor agreement with MP2 values in the H-bonded systems and failed completely for stacked pairs. A similar failure was recently reported for density functional theory calculations on base stacking. It may be concluded that currently available force fields provide much better descriptions of interactions of nucleic acid bases than the semiempirical methods and low-level *ab initio* treatment. © 1997 by John Wiley & Sons, Inc. *J Comput Chem* **18**: 1136–1150, 1997

Keywords: empirical force fields; semiempirical quantum chemical methods; *ab initio* SCF with dispersion energy; H-bonded and stacked DNA base pairs

Introduction

The interaction between nucleotide bases represents an important element in the structure and function of DNA. The H-bonding between guanine (G) and cytosine (C), and adenine (A) and thymine (T) contributes to the stability of the double helix and is responsible for the transfer of genetic information. The role of base stacking is less clear but it certainly plays a role in the stability, variability, and flexibility of the double helix. Most calculations on nucleotides and their complexes are based on empirical energy functions (force fields), which are employed not only in energy minimization but also in computer simulations. Enormous progress in software and hardware in the last several years enables the performance of long molecular dynamics simulations of oligonucleotides.^{1–3} A natural question is how reliable is the structural information obtained by such simulations? One of the important problems in molecular modeling is the ability of empirical potentials to correctly describe interactions of DNA bases. In investigating the way in which various potentials were parametrized, we found a critical lack of reliable data on complexes of DNA bases for testing the force fields. Until very recently only a few experimental and theoretical results existed for base H-bonding^{4–7} and stacking⁸ interactions of nucleic acid bases. The situation changed recently when we published a consistent set of *ab initio* results on all the H-bonded and stacked DNA base pairs^{9a–g} and protonated nucleobase dimers.^{9f} The geometries of H-bonded pairs were optimized at the Hartree–Fock (HF)/6–31G** level while stabilization energies were evaluated⁹ at the beyond HF level utilizing 6–31G* basis sets with flat polarization functions. In the case of stacked

pairs a detail scan of the potential energy surface was made utilizing the same beyond HF procedure as in the H-bonded pairs.

The aim of the present article is to assess the quality of interaction energies of complexes of nucleic acid bases that were obtained by various empirical force fields, semiempirical quantum chemical methods, and the *ab initio* HF method utilizing minimal basis sets of atomic orbitals combined with the London dispersion energy. The reason for testing these various methods is obvious: simulation and modeling of DNA can be performed only by using some less demanding approach than the beyond HF *ab initio* method. If, however, the method of choice fails to give reliable stabilization energies for the DNA base pairs, then its use in DNA simulations is questionable.

The following methods were tested: the empirical force fields AMBER, CHARMM, CVFF, CFF95, OPLS, and Poltev; the semiempirical quantum chemical methods AM1, MNDO/M, and PM3; and the *ab initio* HF method using the MINI-1 minimal basis set combined with the dispersion energy evaluated by the London formula. By using our data one can compare the quality of any other parametrization with both benchmark beyond-HF *ab initio* data and the most popular force fields. Preliminary results concerning H-bonded base pairs were published recently.¹⁰

Methods

EMPIRICAL POTENTIAL FUNCTIONS

All the potentials used are pairwise additive, include internal (bonding) and external (non-bonded) terms, and correspond to all-atom models (all hydrogens are explicitly considered). The non-bonded terms consist of Lennard–Jones and electrostatic parts. The Lennard–Jones part is defined

differently in each potential (see below), while the same expression employing the atom-centered point charges is used for the electrostatic term. None of the potentials used explicitly include the polarization term. A constant dielectric equal to one was employed throughout this study.

AMBER

The AMBER 4.1 program¹¹ with the force field of Cornell et al.¹² was used. This force field¹² was developed for proteins, nucleic acids, and organic molecules. The van der Waals (vdW) interactions were described by the 6–12 term with no consideration of special H-bonded terms. The atomic charges were derived¹² using HF/6–31G* *ab initio* electrostatic potential and restrained electrostatic potential fitting. The HF/6–31G* dipole moments were larger than the experimental ones or those calculated with inclusion of correlation energy^{9d, 9e}; in the case of polar bases this enhancement was about 15%. The electrostatic energy evaluated with the HF/6–31G* charges was therefore also overestimated and this overestimation was considered to compensate for the missing polarization terms.¹² The vdW parameters were obtained¹² from liquid simulations. Some calculations were also performed with the older force field of Weiner et al.,¹³ which is implemented in the Biosym/Discover code.¹⁴ In this case the 6–12 vdW term was augmented by the explicit H-bonding 10–12 term. The atomic charges were derived from a fit to an *ab initio* electrostatic potential evaluated with the HF/STO-3G calculations. Force field parameters for AMBER 3.0 were assigned by AMBER 4.1 code.¹¹ The force field was taken from the dat/oldff3a/parmall.dat file of AMBER 4.1 code; missing parameters for H—N* and CK—N*—H were taken from the AMBER 4.1 force field (parm 94.dat of AMBER 4.1 code). For the Weiner et al.¹³ and Cornell et al.¹² force fields the standard charges for the nucleosides were used with the sugar unit replaced by hydrogen. The hydrogen charge was chosen to neutralize the monomer; the other charges were not changed.

CHARMM

The CHARMM program¹⁵ with empirical energy function parameter set¹⁶ 23 was used. Parameter set 23 is devoted to the simulation of nucleic acids; a parameter set for proteins has been announced in ref. 16, but it has not yet been published. The vdW interactions in CHARMM23 are

described with the 6–12 term but no special H-bonded terms are used. The vdW parameters were obtained from experimental base pairing geometries, *ab initio* interaction energies and geometries between water and the model compounds, and from heats of sublimation of some base analogs. CHARMM23 charges were derived to reproduce the scaled (by a factor of 1.16) HF/6–31G* interaction energies of bases (or base analogs) with water, the dipole moments of the model compounds, and heats of sublimations (if available). The scale factor was used to compensate for the absence of the explicit polarization terms in the CHARMM23.

CFF95

The Biosym/Discover code¹⁴ with implementation of the CFF95 force field¹⁷ was used. The bonding terms in CFF95 were parametrized¹⁸ exclusively using *ab initio* HF/6–31G* quantum mechanical energy surfaces. From distorted molecular structures the energies, energy gradients, and Hessian matrices were evaluated and used for parametrization of the force field.¹⁸ The distorted molecular structures were generated by randomly deforming all the internal coordinates, as well as by systematically rotating about individual bonds. The vdW interactions were described by the 6–9 terms and no H-bonded terms were included.¹⁸ The atomic charges were derived¹⁹ as Cartesian derivatives of molecular quadrupole moments obtained through the HF/6–1G** calculations; the vdW constants were obtained by a fit to experimental crystal structures and sublimation energies.¹⁸ Due to its parametrization method the CFF95 is easily expandable to new systems; the present version includes carbohydrates, hydrocarbons, lipids, nucleic acids, proteins, and complexes of these systems. Some calculations were also performed with an older Biosym force field, CVFF.¹⁴ CVFF atomic charges were derived from the electronegativity and hardness, which were calculated by density functional theory. The CVFF potential utilizes the 6–12 vdW terms and does not use H-bond terms.

OPLS

The Micromodel program²⁰ with the OPLS functions²¹ extended for nucleotide base parameter sets of Pranata and colleagues²² was utilized. The parameter set was developed for the nucleotide bases and 2,6-aminopyridine; parameters for proteins and various functional groups were

included in the original OPLS functions.²¹ The vdW interactions were described by the 6–12 term and no H-bonded terms were used. The OPLS vdW parameters and charges for nucleotide bases were chosen to reproduce the HF/6–31G* *ab initio* geometries and interaction energies of complexes of bases with water; in the case of purine bases the monocyclic model systems were utilized. Because the bonding (intramolecular) terms were not parametrized in the original OPLS function, the merger of OPLS nonbonded potential functions with AMBER bonding potential functions was performed (abbreviation AMBER/OPLS). In AMBER/OPLS the older force field of Weiner et al.¹³ was utilized.

Poltev Potential

The Poltev potential²³ consists of intermolecular terms only. The original version of the potential²³ contained 1–6–12 terms with atom-centered charges derived from the empirical Hückel–Del Re procedure. For H-bonded systems having N–H...O and N–H...N H-bonds the 6–12 potential was replaced²⁴ by the 10–12 one.

SEMIEMPIRICAL QUANTUM CHEMICAL METHODS

The reason for evaluating the semiempirical quantum chemical methods is clear. These methods (contrary to the empirical potentials) allow the breaking of chemical bonds and/or the adding or removing of an electron.

Three recently developed methods based on MNDO approximations,²⁵ namely AM1,²⁶ PM3,²⁷ and MNDO/M,²⁸ were used throughout the paper. Only the last method was explicitly parametrized for H bonding. The PM3 method is known²⁹ to give better results than AM1 for small H-bonded complexes.

NONEMPIRICAL *AB INITIO* METHOD

In the present study, two sets of *ab initio* data of different quality were used.

The benchmark calculations were carried out at a beyond HF level. Interaction energy (ΔE) of the pair was determined as the sum of self-consistent field (SCF) interaction energy and correlation (COR) interaction energy,

$$\Delta E = \Delta E^{\text{SCF}} + \Delta E^{\text{COR}}, \quad (1)$$

where ΔE^{COR} was evaluated using second-order Møller–Plesset theory (MP2). Both interaction energy components were corrected for basis set superposition error using the Boys and Bernardi function counterpoise method.³⁰ All calculations were performed with the medium-sized 6–31G* basis set, where the standard diffuse functions on heavy atoms were replaced by more diffuse ones ($\alpha_d = 0.25$).

Furthermore, we tested the quality of the HF level calculations with a minimal basis set. Interaction energy was evaluated again using eq. (1) with the ΔE^{COR} term approximated by the London dispersion energy. All calculations were carried out with the MINI-1 minimal basis set. For more details see ref. 31.

Results and Discussion

H-BONDED DNA BASE PAIRS

Ab initio beyond HF stabilization energies for all the DNA base pairs^{9b} (cf. Fig. 1) were compared with stabilization energies evaluated at the empirical, semiempirical, and *ab initio* HF levels (data obtained by the Poltev force field were taken from ref. 24). Stabilization energies presented in Table I were obtained as a sum of the MP2 stabilization energy and the HF/6–31G** deformation energy of bases for planar base pairs. The present MP2 stabilization energies differ from those used previously^{9b,g,10} in two items: (i) in contrast to our previous studies, the deformation energy was evaluated with respect to nonplanar optimized bases, which increases the deformation energy by about 0.35 kcal/mol for every guanine molecule; (ii) because many base pairs possess nonplanar structures as the actual minima on the HF/6–31G** potential energy surfaces,^{9d} and because all the tested methods were applied without any geometry constraint, the *ab initio* stabilization energies presented in Table I are further corrected for the energy difference (HF/6–31G**) between nonplanar and planar optimized pairs. For more details see the previous studies.^{9b,9d}

The stabilization energy determined by the empirical and semiempirical methods was defined as the difference between the energy of a base pair optimized in the particular structure and a sum of energies of optimized isolated bases. Energies of isolated bases and base pairs were obtained by gradient optimization using the steepest descent and/or conjugate gradient techniques.

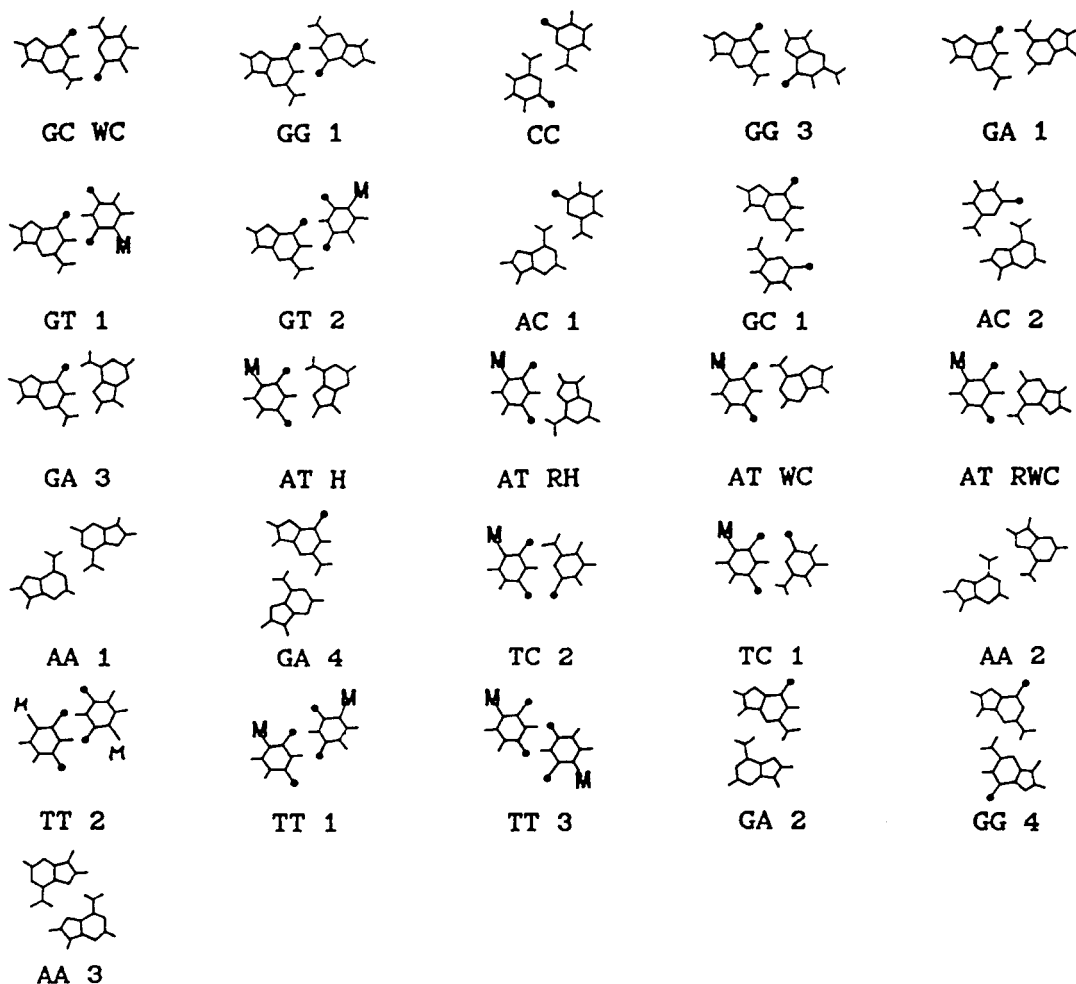


FIGURE 1. Structures of the H-bonded DNA base pairs.

In the case of *ab initio* HF methods the geometries of bases and base pairs were fully optimized with the MINI-1 basis set; here the stabilization energy was evaluated as the sum of BSSE corrected SCF interaction energy and London dispersion energy. Stabilization energies obtained with empirical potentials, semiempirical quantum chemical methods, the *ab initio* HF method, and the *ab initio* beyond HF values are presented in Table I.

The results of linear regression ($Y = A + B \dots X$) and absolute average errors are presented in Table II. Input data for a linear regression represented the set of points (x_i, y_i) , $i = 1, 26$, where x_i is the MP2 stabilization energy for the i th base pair and y_i is the stabilization energy of the same pair obtained by the tested method. The reason for considering the absolute average errors is as follows. Our final goal was to utilize an empirical

potential for the simulation and modeling of DNA and therefore the H-bonding and stacking interactions should be properly balanced. The only possibility of how to ensure this is to keep the interaction energy calculated by the method tested close to the reliable *ab initio* data.

We can see from Table II that surprisingly the best correlation was obtained not for the *ab initio* HF plus dispersion energy method (SCFD) but was for recently introduced empirical potentials; SCFD systematically overestimates the base pair stabilization energy. The reason for "failure" of the SCFD method is, however, understandable.³¹ HF/MINI-1 strongly overestimates the SCF stabilization energy while the London dispersion energy in absolute values is much larger than the respective correlation interaction energy.^{9b}

The original CVFF potential¹⁴ is not considered in Tables I and II due to the fact that it failed to

TABLE I.**Stabilization Energies (kcal / mol) of 26 H-Bonded DNA Base Pairs^a Obtained by *Ab Initio* MP2 Method and Various Empirical Potentials, Semiempirical Quantum Chemical Methods, and SCFD Method**

Base Pair	MP2 ^b	SCFD ^c	A3.0 ^d	A4.1 ^e	CH23 ^f	CFF95	CVFF ^g	OPLS	Pol ^h	AM1	PM3	MNDO / M
GCWC	25.4	33.9	21.2	28.0	25.5	21.3	16.6	23.1	25.5	14.1	14.9	21.5
GG1	24.0	30.9	17.3	26.4	23.6	21.0	16.2	21.4	20.9	14.2	11.9	17.3
CC	18.8	24.9	12.0	18.7	18.1	14.2	10.5	15.1	17.5	8.8	13.2	8.8
GG3	17.1	20.8	15.7	19.4	24.3	16.8	13.6	17.7	18.6	8.8	9.2	13.9
GA1	15.7	21.0	13.3	14.7	15.1	14.9	9.6	12.3	13.4	6.3	8.4	11.3
GT1	14.7	21.5	11.8	16.1	14.0	13.8	10.0	12.9	11.0	8.4	6.2	12.0
GT2	14.3	20.8	11.7	15.6	13.6	12.5	11.6	12.3	13.4	8.3	7.2	12.5
AC1	14.3	19.4	9.5	13.5	12.9	13.0	8.1	9.9	13.7	4.7	8.8	11.4
GC1	13.9	21.9	10.4	15.3	15.1	12.2	9.4	12.3	16.8	6.3	9.8	12.0
AC2	14.1	18.1	11.0	13.7	11.4	14.7	11.7 ⁱ	9.2	13.3	4.4	9.2	11.4
GA3	15.2	18.2	12.1	15.2	13.0	15.1	8.6	11.1	11.9	5.9	7.8	10.9
ATHO	13.3	17.6	11.6	14.5	13.3	12.6	7.9	10.8	11.9	5.5	6.0	11.1
ATRHO	13.2	17.8	11.7	14.5	13.1	12.1	8.3	10.6	11.7	5.5	7.5	11.0
ATWC	12.4	19.1	11.5	12.8	13.6	12.4	8.3	10.5	11.3	5.4	6.9	10.2
ATWRC	12.4	19.4	11.5	12.7	13.5	11.8	8.9	10.3	10.7	5.4	7.1	10.6
AA1	11.5	18.0	7.9	10.8	11.6	11.4	6.7	8.0	16.8	3.3	6.2	9.7
GA4	11.1	18.4	8.1	11.3	11.9	9.7	7.2	9.0	13.2	3.3	6.2	9.8
TC2	11.8	17.5	11.9	12.1	11.1	10.1	9.0	9.6	11.2	6.5	6.1	10.2
TC1	11.6	17.8	11.8	11.8	11.0	9.4	10.0	8.7	9.5	5.2	5.4	10.0
AA2	11.0	15.6	9.2	10.9	10.6	11.2	6.1	7.8	11.1	3.0	5.9	9.6
TT2	10.6	15.2	9.8	12.0	11.2	10.9	7.7	9.6	8.8	7.1	4.9	10.9
TT1	10.6	15.6	9.8	12.1	11.0	10.5	8.3	9.2	9.1	7.1	5.2	10.8
TT3	10.5	16.1	9.8	12.1	10.7	10.3	9.1	8.8	9.7	7.1	5.4	10.7
GA2	10.4	15.5	9.4	11.4	10.8	9.6	6.9	8.9	12.3	2.7	5.6	9.4
GG4	10.3	17.8	7.6	10.7	11.7	7.7	7.0	9.8	13.2	8.8	5.2	8.8
AA3	10.0	12.7	10.5	10.9	9.8	9.1	5.6	7.7	10.6	2.8	4.4	9.0

^aCf. Figure 1.^bRef. 9b.^cHF / MINI-1 + E^D ; ref. 31.^dAMBER 3.0.^eAMBER 4.1.^fCHARMM23.^gCVFF force field with MEP / STO-3G atomic charges.^hPoltev; uracil was considered instead of thymine.ⁱStacked structure.

predict the H-bonded structure as a global minimum for several base pairs. This is in contradiction to the *ab initio* results⁹ showing that the H-bonded pairs are always the most stable. The nonbonded term, specifically the electrostatic energy, plays the dominant role in determining the structure of a pair. The original CVFF force field was therefore combined with atomic charges generated from the molecular electrostatic potential determined with the STO-3G basis set. The modified CVFF yielded more reliable results and now only one pair, AC2, converged to the stacked structure and another one, GG3, had a buckled structure.

Table II shows the largest correlation coefficient for AMBER 4.1 with the Cornell et al. force field,¹² followed by OPLS, CFF95, SCFD, and MNDO/M methods. The correlation coefficient of the CHARMM23 and PM3 methods are still above 0.9. The smallest standard deviation from simple linear regression was again found to be that from the AMBER 4.1 calculations. CFF95, PM3, MNDO/M, and CVFF methods still yielded a standard deviation estimate close to 1 kcal/mol. The smallest values of absolute average error from AMBER 4.1 with the Cornell et al.¹² force field and CHARMM23 were 0.9 and 1.0 kcal/mol, respec-

TABLE II.
Linear Regression $Y = A + BX$ ($X \equiv \Delta E^{\text{MP2}}$) for Various Empirical Potentials and Semiempirical Quantum Chemical Methods.

Method	SCFD ^a	A3.0 ^b	A4.1 ^c	CH23 ^d	CVFF ^e	CFF95	OPLS	Polt ^f	AM1	PM3	MNDO / M
R ^g	0.95	0.89	0.98	0.92	0.88	0.95	0.95	0.85	0.80	0.92	0.95
SD ^h	1.46	1.38	0.93	1.78	1.30	1.05	1.76	2.09	1.79	1.06	1.27
A	4.11	2.35	−0.59	0.14	0.79	1.64	−1.69	1.64	1.79	0.98	3.26
B	1.11	0.66	1.10	1.00	0.62	0.80	0.95	0.85	0.60	0.61	0.58
AAE ⁱ	5.6	2.4	0.9	1.0	4.4	1.2	2.4	1.7	7.3	6.3	2.5

^aHF / MINI-1 + E^{D} .
^bAMBER 3.0.
^cAMBER 4.1.
^dCHARMM23.
^eCVFF with MEP / STO-3G atomic charges.
^fPoltev.
^gCorrelation coefficient.
^hStandard deviation (in kcal / mol).
ⁱAverage absolute error (in kcal / mol); $\text{AAE} = (1 / 26) \sum_{i=1}^{26} |\Delta E^{\text{MP2}} - \Delta E^X|$.

tively; CFF95 gave the still acceptable value of 1.2 kcal/mol. Absolute average errors of semiempirical quantum chemical methods and the *ab initio* SCFD method were larger than those found for empirical potentials.

The relatively “poor” performance of the recently introduced CHARMM23 potential was surprising. Investigating the stabilization energies of individual H-bonded pairs from Table I, we find that CHARMM23 failed completely only in the case of GG3 pair where it strongly overestimated (in comparison with the MP2 method and other potentials) the stabilization energy. CHARMM23 gave a buckled structure (angle between base planes was about 50°) of the pair. The same structure of this pair was found by AMBER 3.0, AMBER 4.1, and CFF95 potentials; the HF method with MINI-1 basis set, on the other hand, predicted the correct planar H-bonded structure. In the case of other H-bonded pairs the CHARMM23 stabilization energies agreed well with the MP2 values. Much better results (cf. Table II) were obtained by performing the correlation analysis without the GG3 pair: $R = 0.97$, $SD = 1.0$, $A = 0.34$, $B = 0.94$, $AAE = 0.8$. Absolute average error was now even better than that of AMBER 4.1 and linear regression results were comparable to those obtained with AMBER 4.1. It should be noted that the GG3 base pairing pattern occurred in the GGC triple H-bonded structure, which belongs to the four basic triple-helix DNA forming triades. The currently revealed problem that CHARMM23 did not satisfactorily reproduce the *ab initio* data for the GG3 base pair may thus influence the model-

ing of the structure and stability of DNA triple helices.

Electrostatic interactions play a dominant role in the H bonding of DNA bases. The derivation of charges in each empirical potential model thus represents a critical step. Two set of charges were shown to be successful: the HF/6–31G* restrained electrostatic potential fit charges (Cornell et al.¹² force field) and charges obtained as Cartesian derivatives of the HF/6–31G** molecular quadrupole moment (CFF95 force field¹⁷). The atomic charges in AMBER 4.1 and CFF95 potentials were derived from the isolated DNA bases while in CHARMM and OPLS the atomic charges were adjusted to fit the properties of complexes of DNA bases with water; the latter charges were originally expected to be more accurate.

STACKED DNA BASE PAIRS

Stacked nucleic acid base dimers differ considerably from the H-bonded pairs because their stabilization comes from dispersion energy that is covered only at the beyond HF level; a gradient optimization with inclusion of electron correlation for systems like DNA base pairs is still impractical. Furthermore, while the optimized geometries of H-bonded base pairs were similar to those found in the crystal structures, stacking geometries observed in crystal structures did not correspond to optimal stacking arrangements.^{9c, 23} Therefore, the strategy for comparison of empirical and semiempirical interaction energies with the nonempirical ones was the following: first the twist dependences

of 10 stacked DNA base pairs were investigated (for the definition of the twist angle and displacement see Fig. 1 in ref. 9c); both bases were coplanar with vertical separation of 3.3 or 3.4 Å, which is the typical distance for stacked bases in DNA. In the next step the dependence of stacking energy on the vertical distance of monomers was studied for all antiparallel (i.e., the twist angle = 180°) homodimers and AA parallel homodimer. Geometries of planar bases, taken from MP2/6-31G* optimizations (U, G, T, A) and MP2/DZ(2d) optimizations (C), were kept frozen in all the methods tested and only the intermolecular coordinates were varied. Structures of the studied stacked DNA base pairs are depicted in Figure 2.

Figure 3 presents the twist dependence of the stacking energy that were determined by AMBER 4.1, CHARMM23, OPLS, and CFF95 empirical potentials and AM1 and PM3 semiempirical methods, together with the data obtained by our MP2-adjusted empirical potential. (This potential closely follows the MP2 values, being within 1.5 kcal/mol of the actual MP2 interaction energies; for more details see ref. 9b.) MNDO/M, which exhibits very similar angular dependences of stabilization energy to the AM1 and PM3 methods, is not shown. In the case of stacked pairs we investigated only those potentials that were successful for H-bonded systems. The agreement between empirical potentials and the *ab initio* data seemed to be worse for base stacking than for H-bonding (see above), although the potentials grossly reproduced the MP2

data. This indicated that the charge distributions and molecular electric potentials of isolated bases were qualitatively correct, because the structure of stacked pairs was determined by the electrostatic term.

In general, the empirical potentials tested exaggerated the dipole-dipole interaction; that is, the difference between energy maxima and minima on the empirical potential twist curves was much larger than those found at the MP2 curve. This overestimation was more pronounced for dimers containing polar guanine and cytosine. The twist dependence of stacking energy of the GC pair is strongly overestimated (compared to the MP2-adjusted potential) by CHARMM23 (by 130%); AMBER 4.1, OPLS, and CFF95 are closer to the MP2 potential. In the case of the CC dimer, all the force fields overestimated the twist dependence (by 100 and 80% for CHARMM23 and AMBER 4.1, respectively). Performance of AMBER 4.1, CFF95, and OPLS was similar for the GC pair, while CHARMM23 strongly overestimated (by about 8 kcal/mol) stabilization energies in the 0° region of the twist angle. OPLS and CFF95 underestimated the binding energy of the AA stack. For this pair AMBER 4.1 and CHARMM23 closely mimicked the MP2-adjusted potential, but CHARMM23 exaggerated stabilization only in the 180° region of the twist angle. Similar underestimation of the OPLS binding energy was also found in case of the GA pair. For the AC pair again CHARMM23 gave the worst results and CU AMBER, CHARMM23,

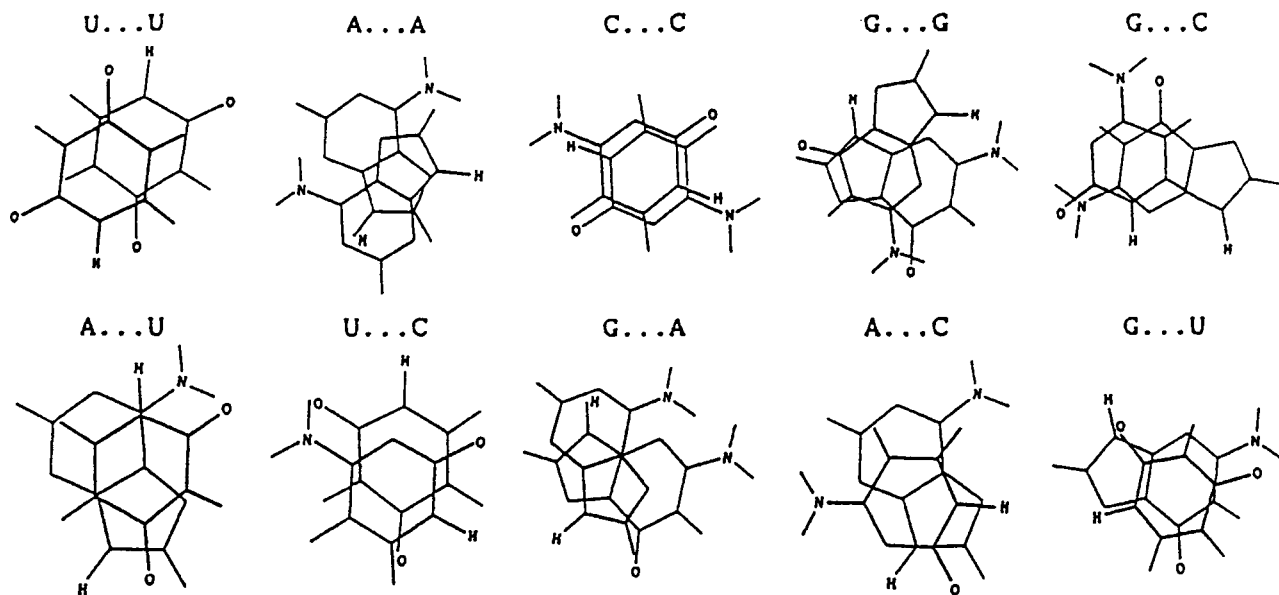
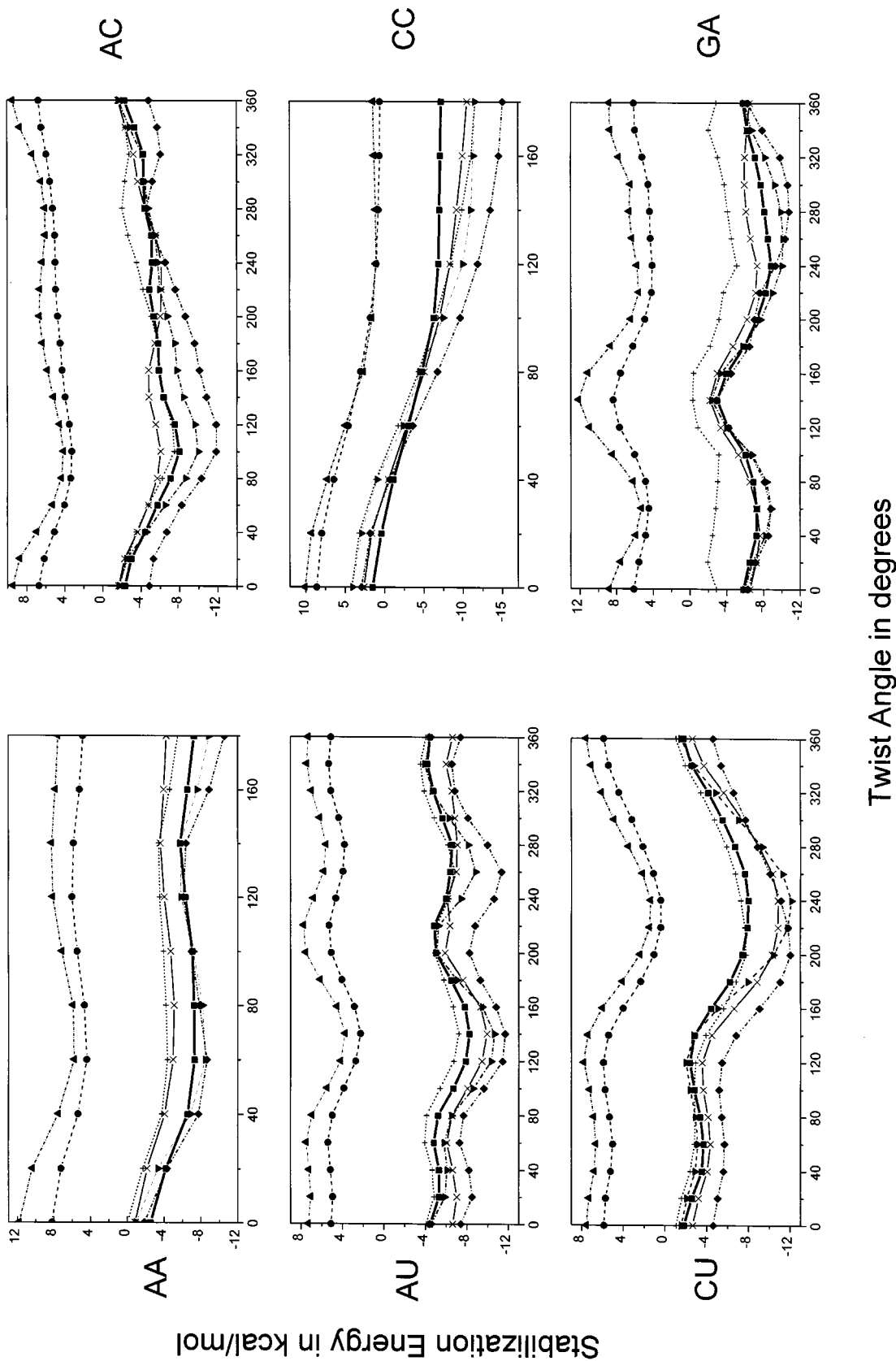


FIGURE 2. Structures of the stacked DNA base pairs with optimized twist and displacement (ref. 9c, Fig. 3).



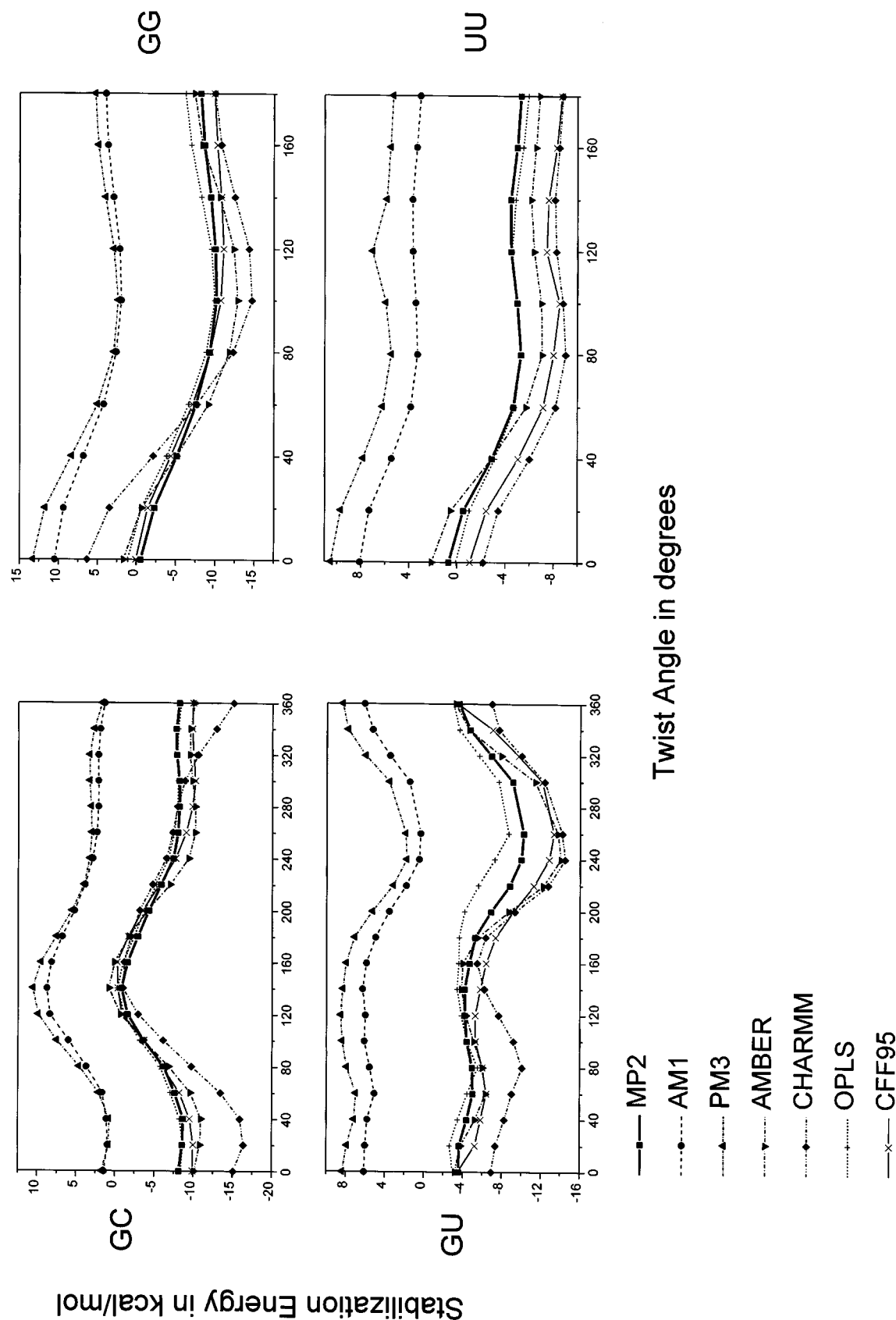


FIGURE 3. Twist dependence of stacking energy for various DNA base pairs.

and CFF95 gave too deep a minimum near the twist angle of 240°; here OPLS agreed fairly well with MP2 data. CHARMM provided the largest deviation also for the AU and GU stacks; in both cases OPLS again agreed fairly well with the MP2 potential. In general, the largest differences with respect to MP2 data were found for the CHARMM23 force field; the performance of AMBER 4.1, CFF95, and OPLS were mostly similar.

Both semiempirical quantum chemical methods gave too repulsive interaction energies; however, their angular dependence was correct (cf. Fig. 3). The shift of interaction energies was rather monotonous and equal to as much as 10 kcal/mol, which was what made the use of these semiempirical quantum chemical methods for DNA simulations questionable.

The ability of empirical potentials to correctly reproduce the dependence of stacking energy on vertical separation of bases is an important feature of any empirical potential. Previous research showed that many empirical potentials used in conformational studies on DNA fail to reproduce the observed separation of base pairs, which may lead to incorrect results.^{32a,32b}

Vertical separation was optimized for antiparallel structures of AA, CC, GG, and UU stacked pairs, and parallel structure of the AA pair. The respective stabilization energies and distances are collected in Table III. The four potentials slightly exaggerated the optimal vertical separations compared to the MP2 values; larger deviation was found for OPLS. This overestimation was, however, rather small; in addition antiparallel dimers belong to those structures where *ab initio* data indicated reduced short-range repulsion.^{9c,9e} The

situation with absolute values of stabilization was different. In the AA pair parallel structure the agreement between MP2 and empirical potentials was very good. For the antiparallel AA structure the AMBER 4.1 result was close to the MP2 values; CHARMM23 overestimated and OPLS and CFF95 underestimated stabilization. All force fields exaggerated the stabilization for the CC dimer, which was especially evident for the CHARMM23 potential. This force field even underestimated the optimal vertical separation in the cytosine dimer. Stabilization energies of GG and UU pairs evaluated by all four potentials did not differ dramatically from the MP2 values. Best results for the former pair yielded CHARMM23 and CFF95, for the latter one AMBER 4.1.

Figure 4 shows the dependence of vertical distance on stabilization energy for the antiparallel structure of the CC stacked pair. All the potentials overestimate repulsion at shorter distances of bases; the shape of CFF95 and AMBER 4.1 curves is similar to that of MP2 stabilization energy. The overestimation of the CHARMM23 stabilization energy is also evident.

Vertical dependences were not investigated for semiempirical quantum chemical methods, which were shown to give unrealistically repulsive interaction energies for all the stacked pairs (see above).

B-DNA DECAMER

A global test of the performance of various empirical potentials was carried out by evaluating all the base–base interactions in a B-DNA decamer. The semiempirical quantum chemical methods were not tested because they failed for

TABLE III. Stabilization Energies (ΔE ; kcal / mol) and Optimized Distances (R ; Å) for Antiparallel Structures (AA also for Parallel Structure) of Stacked DNA Base Pairs Obtained by *Ab Initio* Calculations and Various Empirical Potentials

Base pair ^a	MP2 ^b		A4.1 ^c		CFF95		CH23 ^d		OPLS	
	ΔE	R	ΔE	R	ΔE	R	ΔE	R	ΔE	R
A-A	8.3	3.3	9.2	3.4	5.5	3.6	10.6	3.4	7.4	3.6
C-C	8.3	3.3	11.1	3.4	10.3	3.3	15.1	3.2	11.7	3.4
G-G	9.1	3.3	7.4	3.5	10.0	3.5	9.9	3.4	7.2	3.6
U-U	6.1	3.3	6.9	3.4	8.5	3.4	8.7	3.3	6.8	3.5
A-A parallel	3.6	3.6	3.3	3.7	3.4	3.7	3.6	3.6	3.9	3.8

^a cf. Figure 2.
^b Ref. 9c.
^c AMBER 4.1.
^d CHARMM23.

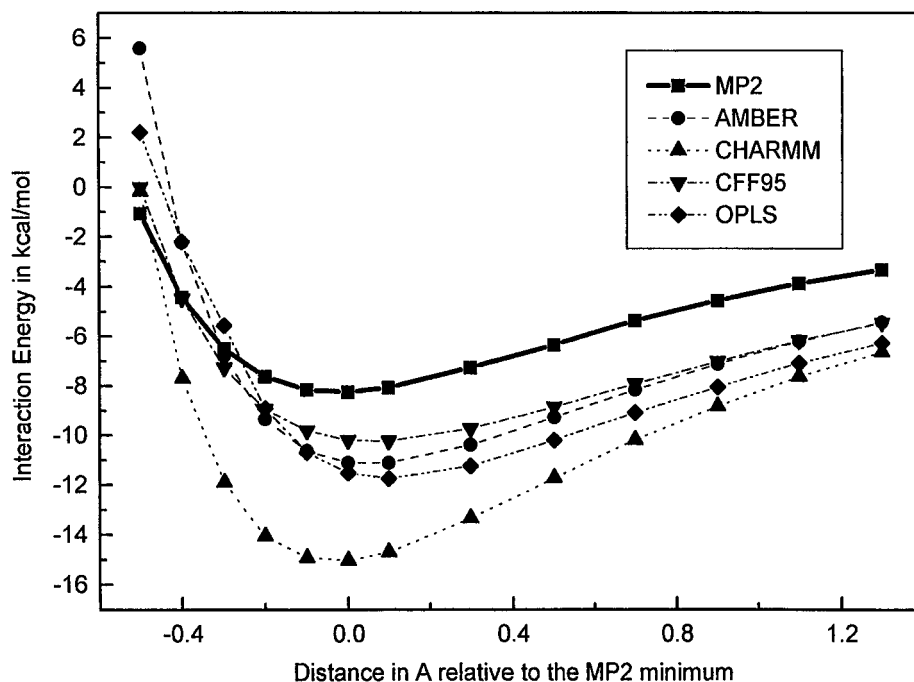


FIGURE 4. Dependence of stabilization energy on vertical distance of the antiparallel CC stacked pair.

stacked pairs (see above). Only those empirical potentials tested for the twist dependence were considered. The CCAACGTTGG B-DNA decamer³³ was refined to a resolution of 1.4 Å; the crystal was of the C_2 space group. Only the DNA bases were considered; that is, all the atoms of sugar-phosphate units were neglected. The C_1 carbon of a sugar unit was replaced by hydrogen; the C_1H distance was not adjusted. The computational procedure thus differed slightly from our previous study,^{9c} where optimized bases were superimposed over crystal data. The structure of the decamer and numbering of bases is depicted in Figure 5. The total stabilization of the decamer consists of 10 H-bonding energies, 18 intrastrand stacking energies, and 18 interstrand stacking energies. MP2 nonempirical *ab initio* stabilization energies as well as empirical potential stabilization energies are presented in Table IV.

Table IV shows that all four potentials reproduce H-bonding satisfactorily; OPLS and CFF95 slightly underestimate stabilization energies while AMBER 4.1 slightly overestimates the GC stabilization energies. Also the MP2 intrastrand-stacked and interstrand-stacked stabilization energies are basically reproduced by empirical potentials. Notice the very good agreement in the case of repulsion contributions of C5T17 and C5C15 pairs. For

the C1C2 stacked pair, the MP2 method gives zero stabilization while all four potentials predict slight destabilization. The largest deviation is found for CHARMM23 for G9G10 and G6G16 pairs. Linear regression analysis performed for intrastrand-stacked and interstrand-stacked base pairs (cf. Table V) shows that AMBER 4.1 gives the best results from all the potentials tested and its absolute average error is the smallest. Performance of

C₁ ... G₂₀
 C₂ ... G₁₉
 A₃ ... T₁₈
 A₄ ... T₁₇
 C₅ ... G₁₆
 G₆ ... C₁₅
 T₇ ... A₁₄
 T₈ ... A₁₃
 G₉ ... C₁₂
 G₁₀ ... C₁₁

FIGURE 5. Structure and numbering of the B-DNA decamer.

TABLE IV.
Stabilization Energies^a (kcal / mol) for CCAACGTTGG
B-DNA Decamer Obtained by *Ab Initio* MP2
Method and Various Empirical Potentials

Base Pair ^b	MP2	A4.1 ^c	CFF95	CH23 ^d	OPLS
A3T18 (H)	13.4	12.8	11.7	13.4	10.4
A4T17 (H)	13.2	11.9	11.0	12.6	9.7
C1G20 (H)	24.5	28.4	21.6	24.5	22.7
C2G19 (H)	26.0	28.8	22.1	25.8	23.1
C5G16 (H)	27.6	28.4	21.8	25.5	23.2
A3A4 (S)	6.3	6.1	3.9	5.4	4.0
A4C5 (S)	4.8	4.5	2.9	5.4	3.2
C2A3 (S)	2.4	1.8	0.8	1.2	1.2
C1C2 (S)	0.0	-1.9	-1.4	-2.1	-2.5
C5G6 (S)	5.3	8.0	5.5	3.2	4.4
G9G10 (S)	2.9	1.2	2.1	-4.0	0.0
G6T7 (S)	4.9	6.0	5.9	6.6	5.4
T8G9 (S)	6.0	7.9	7.9	6.9	4.9
T7T8 (S)	3.0	3.2	4.1	4.1	5.4
A3G19 (I)	2.7	3.5	4.0	3.9	3.6
A4T18 (I)	0.9	1.1	1.2	1.3	1.1
C2G20 (I)	3.5	4.6	4.7	5.5	3.8
C5T17 (I)	-0.2	-0.7	-0.2	-0.6	-0.6
G6G16 (I)	4.6	5.0	7.0	11.6	5.6
A4G16 (I)	4.5	5.0	6.7	5.5	3.8
A3T17 (I)	1.9	2.6	5.4	2.7	2.1
C5C15 (I)	-1.4	-2.0	-1.2	-2.4	-1.7
C1G19 (I)	5.4	6.5	5.9	7.9	5.0
C2T18 (I)	2.5	3.2	3.9	4.4	3.2
Σ H	209.4	220.5	176.4	205.9	178.2
Σ S	71.0	73.9	63.4	53.2	52.0
Σ I	48.8	57.6	74.8	79.6	51.8
Σ H + S + I	329.2	352.0	314.6	338.7	282.0

^aNegative sign means destabilization.
^bFor definition see Figure 5; symbols (H), (S), and (I) characterize the base pair and stand for H-bonded, intra-strand-stacked, and interstrand-stacked orientation.
^cAMBER 4.1.
^dCHARMM23.

OPLS and CFF95 potentials is similar. CHARMM23 gives the largest deviations. The total MP2 H-bonding, intrastrand-stacking, and interstrand-stacking energies (cf. Table IV) are best reproduced by AMBER 4.1; all the contributions are systematically slightly overestimated. CFF95 underestimates H-bonding and intrastrand-stacking but overestimates the interstrand-stacking; OPLS exhibits similar behavior. CHARMM23 reproduces H-bonding well but strongly underestimates intrastrand stacking and overestimates interstrand-stacking. The sum of all base–base interactions provided by CHARMM23 is very close to the MP2 data (the closest among all the potentials). However, the balance between the various contri-

TABLE V.
Linear Regression $Y = A + BX$ ($X \equiv \Delta E^{\text{MP2}}$) for
Various Empirical Potentials for Intrastrand-Stacked
and Interstrand-Stacked Base Pairs in B-DNA
Decamer

Potential	A4.1 ^a	CFF95	CH23 ^b	OPLS
R ^c	0.95	0.83	0.75	0.84
SD ^d	0.95	1.61	2.66	1.37
A	-0.62	0.37	-0.68	-0.28
B	1.29	1.03	1.32	0.95
AAE ^e	0.9	1.3	1.9	1.0

^aAMBER 4.1.
^bCHARMM23.
^cCorrelation coefficient.
^dStandard deviation (kcal / mol).
^eAverage absolute error (kcal / mol); AAE = $(1 / 19) \sum_1^{19} |\Delta E^{\text{MP2}} - \Delta E^*|$.

butions (see above) is not properly reproduced by CHARMM23 and may lead to an imbalanced description of the interactions in DNA.

RELIABILITY OF PRESENT *AB INITIO* MP2 CALCULATIONS

The reliability of the present comparative study, and those made in the future, depends on the quality of the benchmark data. Let us estimate the accuracy of the stabilization energies evaluated at the MP2 level with the 6–31G* basis set having diffuse polarization functions. Pilot CCSD(T) calculations with the cc-pVDZ basis set performed by us for the CC and UU H-bonded pairs indicate that MP2 and CCSD(T) H-bonding energies are very close. Similar results were obtained with the aug-cc-pVDZ basis set for model complexes such as H-bonded cyclic formamide and formamidine dimers.³⁴ On the other hand we are aware that 6–31G*(0.25) as well as cc-pVDZ basis sets underestimate the correlation interaction energy with respect to larger basis sets. We thus expect that the present *ab initio* H-bonding energies slightly underestimate the actual H-bonding energies. In the case of base-stacking interactions, the MP2/6–31G*(0.25) calculations provide an accurate description of the structure-making electrostatic energy.^{9c,9e} The situation is much less clear as far as the dispersion attraction is concerned. Basis set extension would lead to larger dispersion stabilization. On the other hand, the higher order correlation contributions are expected to be repul-

sive. This is confirmed by all CCSD(T) and MP4(SDTQ) calculations performed so far on aromatic-stacking complexes: benzene...Ar,³⁵ benzene dimer,³⁶ aminopyridine dimers,³⁷ pyrimidine dimer,³⁷ pyridine dimer,³⁷ and triazine dimer.³⁷ In all these cases the MP2 stabilization energy was larger than the CCSD(T) one. Thus, the present MP2/6-31G*(0.25) base pair stacking energies are believed to be close to the actual stacking energies.

Conclusion

1. Among all the tested methods, AMBER 4.1 with the force field of Cornell et al.¹² best reproduces the *ab initio* H-bonding and stacking stabilization energies for both optimized and crystal geometries.
2. The *ab initio* SCFD method systematically overestimates stabilization energies of H-bonded base pairs.
3. The correlation between MP2 and semiempirical quantum chemical stabilization energies for 26 H-bonded pairs is poor, with the best results obtained with the MNDO/M method. In the case of stacked pairs the semiempirical quantum chemical methods give interaction energies that are too repulsive.
4. Recently introduced force fields provide a better description of the interaction energies of neutral nucleic acid base dimers than any molecular orbital technique of a quality lower than the MP2 procedure. However, the HF method with minimal basis set yields reasonable geometries and stabilization energies of H-bonded pairs and never fails completely as does CHARMM23 with the GG3 base pair.

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